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(54) Controlled-release rectal pharmaceutical preparation.

(57) A controlled-release pharmaceutical preparation of 3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine. The controlled-release preparation is in the form of rectal suppository containing 3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine. Further the controlled-release is prepared by implanting 3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine in an oleaginous base.

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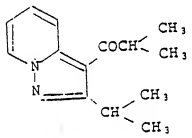
CONTROLLED-RELEASE RECTAL PHARMACEUTICAL PREPARATION

This invention relates to pharmaceutical preparations exhibiting a controlled-release of 3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine (Code No. KC-404), and its use for effecting a vasodilating or bronchodilating action.

KC-404, the molecular weight being 230.0, has the chemical structure as described below. It is a white crystalline powder having a melting point of 51 - 54°C, and is well soluble in chloroform and ethanol, but almost insoluble in water.



KC-404 is a therapeutically useful compound having a cerebral vasodilating and bronchodilating action as disclosed in JP-A-52-29318. Nausea and vomiting were, however, caused by KC-404 when orally taken as bulk powder.

Development of the side effects seemed to be associated with the sudden increase of KC-404 serum concentration, because they developed in the early stage just after the dose was given and not at a later stage, and the time of development coincided with that of the initial increase in the serum concentration. It is therefore an important object of this invention to develop well controlled-release preparations of KC-404 and production methods thereof, to control the sudden increase of serum concentration.

This invention provides rectal suppositories as therapeutically useful controlled-release preparations of KC-404.

As a base for rectal suppositories, oleaginous bases were the most suitable for controlled-release suppositories of KC-404 among water soluble, oleaginous and emulsion-type bases.

Oleaginous bases like cocoa butter and water soluble bases like polyethylene glycol can be utilized to produce suppositories, but oleaginous bases are the most suitable for controlled-release suppositories of this invention. As the oleaginous base, cocoa butter, Witepsol^{R} (Dynamite Novel Co., Ltd.), Novata^{R} (Henkel Hakusui Co., Ltd.), plant oils, animal fats and fatty acids and a mixture thereof can be used. In accordance with this invention, the controlled-release suppositories can be prepared by cooling the molten mixture of KC-404 and the bases in a plastic container for suppositories, or by formulating the KC-404 solution in plant oil into soft rectal capsules.

Rectal absorption and the development of side effects were investigated with controlled-release suppositories obtained in this invention by healthy volunteers. The volunteer test was performed as follows. Administration: rectal administration of suppositories containing 20 mg of KC-404. Assay: mass-fragmentography.

As shown in Fig. 1, the controlled-release suppositories of KC-404 produced in this invention using oleaginous bases exhibited a gradual increase in the serum level to 6 hrs. and maintained the level up to at least 15 hrs. after the dose was given to the healthy volunteers. This suppository was of a very safe dosage, as there was no development of nausea or vomiting in three subjects.

Fig. 1 shows the serum level profile in healthy volunteers who received suppositories containing 20 mg of KC-404, which were prepared as in Example 1.

The invention will be cescribed in greater detail in conjunction with the following specific examples, but the invention should not be regarded as being limited thereto.

Example 1:

0.51 g of KC-404 was dissolved in 49.5 g of Witepsol^{R} W-35, which had been preheated and melted at 45°C. Each 1.95 g of the resulting molten mass was cooled down to room temperature in a plastic container for suppositories containing 20 mg of KC-404. The serum level in healthy volunteers resulting from this suppository displayed a gradual increase for 6 hrs. after the dose was given and maintained the level up to 15 hrs. after the dose was given (Fig. 1).

Example 2:

24.99 kg of Witepsol^{R} W-35 was melted at 60°C and then 391 g of KC-404 was dissolved therein. The resulting molten mass was injected into a plastic container for suppositories by an automated manufacturing machine for suppositories, maintaining a temperature of about 33°C, and the solidefied by cooling at 20 - 18°C and sealed. Each suppository contained 20 mg of KC-404, weighing 1.3 g.

Example 3:

24.96 kg of Witepsol^{R} W-35 was melted at about 60 °C and then 194 g of KC-404 was dissolved therein. The resulting molten mass was injected into a plastic container for suppositories by an automated manufacturing machine for suppositories, keeping the temperature at about 37 °C, and then solidified at 20 - 18 °C and sealed. Each suppository contained 10 mg of KC-404, weighing 1.3 g.

Example 4:

2 g of KC-404 was dissolved in 78 g of Witepsol^{R} H preheated at about 43 °C, and injected into a plastic container for suppositories to be 0,8 g as a net weight, and then solidified at ambient temperature.

Example 5:

2 g of KC-404 was dissolved in 78 g of Witepsol^{R} E preheated at about 55 °C, and the resulting molten mass was injected into a plastic container for suppositories to be 0.8 g as a net weight, and then solidified at ambient temperature

Claims

1. A conontrolled release rectal suppository containing 3-isobutyryl-2-isopropylpyrazolo[1,5-a]-pyridine is in an oleaginous base.

2. The suppository of claim 1 wherein the oleaginous base is cocoa butter, a plant oil, animal fat, fatty acid, or a mixture thereof.

3. A method for preparing the rectal suppository of claim 1 which comprises mixing 3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine with a molten oleaginous base and then cooling the mixture to form suppositories.

4. The suppository according to clain 1 or 2 for use in effecting a vasodilating or bronchodilating action in a human subject while avoiding nausea or vomiting side effects in said subject.

FIG. 1